REMARKS

Claims 40-44, 48-62 and 64 are pending in this application. Claims 54-59 and 64 are withdrawn from consideration, as being directed to a non-elected invention. Claims 40-44, 48-53 and 60-62 stand rejected. Applicant would like to thank the Examiner for the interview conducted on December 1, 2004 with Applicant and Applicant's attorney. During said interview, Applicant pointed out the difference in homology between human and chimpanzee framework regions with respect to each other and rodent. The Examiner provided useful comments for this response that are incorporated herein. No claims are amended in this response. However, Applicant provides all current claims herein with status identifiers for the convenience of the Examiner.

OBJECTION TO THE CLAIMS

Claims 49-50, 52-53, 60-62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form. Applicant respectfully submits that he has overcome the Examiner's rejection of claims 40-44, 48 and 51 below and requests that objection to claims 49-50, 52-53, 60-62 be withdrawn.

35 U.S.C. § 103

Claims 40-44, 48, and 51 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Adair, *et al.* (WO 91/09967, published 7/11/91) in view of Vijh-Warrier, *et al.* (*Molecular Immunology* 32:1081-1092, 1995) and Queen, *et al.* (U.S. Patent No. 5,693,762). The Examiner alleges that one of ordinary skill in the art would have been motivated to and have a reasonable expectation of success to produce the claimed invention because, "Vijh-Warrier, *et al.* teach that chimpanzee mAbs are no more likely to elicit deleterious anti-immunoglulin response in humans than are human mAbs and that chimpanzee VH and Vk genes are no more divergent than the human genes." The Examiner relies further on the teachings of Adair, *et al.*, Queen, *et al.*, and Co, *et al.* alleging that these references teach the skilled artisan how to make substitutions in the human framework region of a chimerized antibody to obtain the affinity of the "parent antibody."

Applicant respectfully traverses this rejection. Applicant respectfully submits that for a proper obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of

establishing *prima facie* with evidence or reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

The Examiner alleges, "it would have been *prima facie* obvious to have used the framework regions from *Pan troglodyte* to produce immunoglobulin amino acid sequences and combine the teachings of Adair, *et al.* and Queen, *et al.* and Co, *et al.* who has produced antibodies with rodent CDRs and combine this with chimpanzee frameworks due to the high homology between chimpanzee mAbs and human mAbs as taught by Vijh-Warrier, *et al.*" Applicant concedes that, in general, human and chimpanzee genomes show high homology when most regions of genomes from the two species are compared. However, as is discussed below, a greater divergence between human and chimpanzee is observed in regions encoding variable domains, including framework only regions. Furthermore, as the Applicant discussed with the Examiner at the interview conducted on December 1, 2004, raising antibodies to human antigens in chimpanzee has certain limitations, because of the high homology between human and chimpanzee genomes in general. For instance, a chimpanzee immune system may recognize a human antigen as a self antigen, thereby not producing antibodies to it or producing antibodies to it with a low binding avidity.

In addition, the Examiner appears to assume that human and chimpanzee genomes share high homology throughout, including the immunoglobulin variable regions. Applicant teaches in the instant specification that the variable region of chimpanzee compared with human is more divergent than are other regions of the chimpanzee and human genomes. For instance, at pages at page 12, lines 37-43, Applicant discloses that the overall sequence homology between chimpanzee and human VH regions range from 76% to 95% sequence identity, with a mean identity of about 84%. Applicant also teaches, as was discussed at the interview, this divergence in variable region sequences can be used to expand the repertoire of acceptor framework regions in producing chimeric antibodies. By contrast, Vijh-Warrier, *et al.* merely suggests using antibodies raised in chimpanzees for passive immunotherapy to

reduce immunogenicity in humans, assuming that variable regions from chimpanzee will be highly homologous to those of humans. Thus, Applicant respectfully submits that Vihj-Warrier, *et al.* do not teach or suggest raising antibodies in rodents to human antigens to make chimeric antibodies. Nor, do they teach or suggest that variable regions for primates may be divergent from human while still providing reduced immunogenicity in chimeric antibodies.

Furthermore, the Examiner alleges that because Adair, *et al.*, Co, *et al.*, and Queen, *et al.* teach humanizing antibodies from rodents, and because human and chimpanzee genome are homologous, using variable regions from primates would be obvious. Applicant respectfully submits that as discussed above, the variable regions of chimpanzee and human diverge. Furthermore, as described in the specification, and discussed at the interview, primate variable regions of the instant invention are selected by comparing rodent variable regions with primate variable regions for the closest homology. As is demonstrated in the specification, a comparison of the most homologous variable region from primate compared with rodent does not necessarily select the variable regions from chimpanzee that are closest in homology to human. For instance, at page 23, lines 8-14, Applicant describes the selection of variable heavy chain region from chimpanzee with variable heavy chain from rodent for anti-integrin antibody. The selected region showed about 53% homology between rodent and chimpanzee. Furthermore, when the selected region from chimpanzee is compared with human, the homology between human and chimpanzee is only 84%; see page 12, Table 1 of the specification. Thus, Applicant respectfully submits that selecting a variable region from primate will not produce results that are the same as selecting against a human framework. In fact, the selection may not provide a variable region that is homologous to human. Thus, the instant invention expands the possible repertoire of variable regions for chimeric antibodies beyond those contemplated by the art.

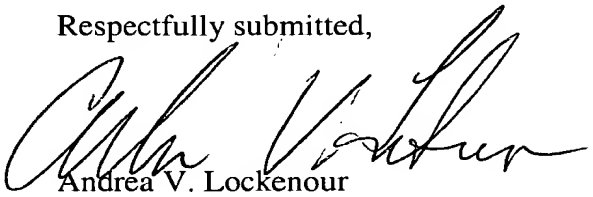
In summary, Applicant respectfully submits that the Examiner has met neither prong of his burden required by *In re Vaeck, supra* for the following reasons. Vijh-Warrier, *et al.* do not suggest using primate variable regions in combination with rodent CDRs. As the Examiner indicates, Vijh-Warrier, *et al.*, rely on creating mAbs to human antigens in primates that will have variable regions of high homology to human mAbs. As is discussed above, although most regions of human and primate genomes are homologous, the variable regions of humans and primates diverge. Thus, based on the teachings of Vijh-Warrier, *et al.*,

the skilled artisan would not have a reasonable expectation of success in creating a chimeric antibody having framework regions that diverge from human and still having reduced immunogenicity. Furthermore, Adair, *et al.*, Queen, *et al.* and Co, *et al.* only teach using variable regions from humans in combination with rodent CDRs. As is discussed above, the variable regions of chimpanzee and human diverge. Furthermore, the antibodies described in the instant application are made by comparing the variable regions of donor rodents with acceptor primate, which often leads to selection of variable regions having less homology than a rodent-human comparison. Thus, none of the references, either alone or in combination, provide the skilled artisan with an expectation of success of creating a chimeric antibody using primate frameworks, which may be less homologous to rodent than human, yet have reduced immunogenicity.

Applicant respectfully submits that in view of the forgoing remarks, he has overcome the Examiner's rejection of claims 40-44, 48 and 51 under 35 U.S.C. § 103. Reconsideration and withdrawal of these rejections is respectfully requested.

Applicant reserves the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the cancelled claims, the claims as originally filed, and any other claims supported by the specification. Applicant thanks the Examiner for the Office Action and believes this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned attorney.

Respectfully submitted,



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